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Antiviral Classification

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Nomenclature

EC_{50} The concentration of a drug inducing its half-maximal effective response.

IC_{50} The concentration of an inhibitor at which 50% of inhibition in its activity is achieved.

Glossary

Allosteric inhibitors Inhibitors block the enzymatic activity by targeting outside the active site of viral enzymes.
Antiviral drug resistance The reduction in the effectiveness of an antiviral agent to treat an infectious disease, probably caused by amino acid mutations within or outside the drug-binding site.
Drug susceptibility The sensitivity of viruses to one or more drugs. If a virus is susceptible, it can be treated with the drug.
Genetic barrier to resistance The threshold above which drug resistance develops to a drug or a drug class.
HAART Highly active antiretroviral therapy which contains a combination of ≥ 3 antiretroviral drugs.

Introduction

During the past decades, more than 100 antiviral agents or their combinations have been approved to treat 9 human infection diseases: HIV, HCV, influenza virus, RSV, HSV, HCMV, VZV, HBV, and variola virus (human smallpox). Antiviral agents can be possibly classified based on their chemical structures, drug targets, or mechanisms of action. For instance, most antiviral agents target either viral enzymes to block the viral replication or viral surface proteins to prevent the viral entry. Regarding the mechanisms of action, nucleoside analogs are effective viral polymerase inhibitors that resemble naturally occurring nucleosides to cause the termination of the nascent viral DNA chain, while protease inhibitors block the proteolytic processing by competing with protease substrate peptides. Based on the chemical structures, aciclovir and valaciclovir are classified as acyclic guanosine analogs to treat DNA viruses such as HSV and VZV, while cidofovir, adefovir, tenofovir alafenamide are acyclic nucleoside phosphonate analogs to treat HCMV, HBV, and HIV, respectively. Due to the variable nature of antiviral agents, this book article attempts to characterize the antiviral classification based on the drug targets in 9 human infectious diseases.

Human Immunodeficiency Virus (HIV)

HIV Reverse Transcriptase

HIV reverse transcriptase (RT) is an asymmetric heterodimer which harbors two enzymatic domains: the RNA- and DNA-dependent DNA polymerase and the ribonuclease H (Li and De Clercq, 2016). After the viral entry of HIV particles, HIV RT produces the viral DNA genome based on the template of the single-stranded viral RNA genome released from HIV particles (Das *et al.*, 2019). To inhibit HIV genome replication, nucleoside RT inhibitors (NRTIs) and non-nucleoside RT inhibitors (NNRTIs) have been successfully developed to target HIV RT – an indispensable enzyme for HIV replication. On the one hand, the 5′-triphosphate of the NRTIs act as chain terminators. Because NRTIs lack a 3′-OH group, the incorporation of NRTIs into the newly synthesized viral dsDNA terminates the elongation of DNA primer, thereby blocking HIV reverse transcription (Das and Arnold, 2013). On the other hand, NNRTIs are allosteric inhibitors that allosterically target a hydrophobic pocket located approximately 10–15 Å from the catalytic site of HIV-1 RT (Sluis-Cremer and Tachedjian, 2008). This causes conformation changes of the HIV-1 RT catalytic site, thus interrupting the viral dsDNA replication (De Clercq and Li, 2016).

As of September 2020, fifteen HIV RT inhibitors have been approved by the US FDA for clinical use, including (1) seven NRTIs: zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, emtricitabine; two NtRTIs (nucleotide RT inhibitors): tenofovir disoproxil fumarate and tenofovir alafenamide; and (2) six NNRTIs: nevirapine, delavirdine, efavirenz, etravirine, rilpivirine, and doravirine. Elsulfavirine has only been approved in Russia. For more than two decades, NRTIs have been clinically used as the backbone in the highly active antiretroviral therapy (HAART, a combination of ≥ 3 antiretroviral drugs), while NNRTIs often serve as the third agent. Currently, tenofovir alafenamide and doravirine are widely administered in clinical practice because of a high genetic barrier to resistance, high safety profile, and low frequency of administration (Deeks, 2018; De Clercq, 2018). Novel RT inhibitors such as islatravir and dapivirine are currently under development (Baeten *et al.*, 2016; Nel *et al.*, 2016; Nakata *et al.*, 2007).

HIV Protease

HIV protease plays an indispensable role in the proteolytic processing of Gag and Gagpol polyproteins to release key structural proteins (matrix, capsid, nucleocapsid, p6) and viral enzymes (reverse transcriptase, integrase, protease) (Li and De Clercq, 2016). HIV protease is a homodimer of two subunits and the active site of HIV protease is located at the center of the substrate-binding tunnel. This substrate-binding tunnel has been recognized as a conserved drug-binding pocket for the development of HIV protease inhibitors to prevent proteolytic processing (Ko *et al.*, 2010).

As of September 2020, 10 protease inhibitors have been approved by the US FDA. The era of protease inhibitors began in 1995 when saquinavir was the first protease inhibitor approved for clinical use. Subsequently, the US FDA approved ritonavir (a protease inhibitor and pharmacokinetic booster) in 1996, indinavir in 1996, nelfinavir in 1997, amprenavir in 1999, lopinavir and atazanavir in 2000, fosamprenavir in 2003, tipranavir in 2005, and darunavir in 2006. Over the past decades, HIV protease inhibitors have become an important ingredient of HAART (Hammer *et al.*, 1997; Gulick *et al.*, 1997). Nevertheless, the rapid emergence of resistance and poor bioavailability pose a challenge to the clinical use of protease inhibitors (Subbaiah *et al.*, 2017). Currently, darunavir is the most popular protease inhibitor (Deeks, 2014), while saquinavir and amprenavir have been virtually discontinued (De Clercq and Li, 2016).

HIV Integrase

HIV integrase, encoded by the HIV Pol gene, is an indispensable enzyme for integrating viral DNA genomes into human chromosomes by a series of DNA cutting and joining reactions (Asante-Appiah and Skalka, 1999; Esposito and Craigie, 1999). Since the viral DNA synthesized by HIV reverse transcriptase is initially blunt-ended, there are two critical steps of viral integration: (1) the 3′ end processing reaction removes two nucleotides from each of the 3′ ends of the viral dsDNA before viral integration; and (2) the DNA strand transfer reaction that breaks the human chromosome and 3′ ends of viral DNA are joined to the 5′ ends of human chromosome at the integration sites (Li *et al.*, 2015). Antiviral compounds have been screened to inhibit either the 3′ end processing reaction or the DNA strand transfer reaction (Delelis *et al.*, 2008). Compounds against the 3′ end processing reaction are inactive, but integrase strand transfer inhibitors (INSTIs) have shown potent antiviral activities in both in vitro and in vivo studies (Delelis *et al.*, 2008). INSTIs selectively bind near the 3′ end of the viral DNA in the structural complex of viral DNA and HIV integrase, thereby blocking the DNA strand transfer reaction (Delelis *et al.*, 2008).

As of September 2020, four INSTIs (raltegravir, elvitegravir, dolutegravir, bictegravir) have been approved by the US FDA. The first-generation INSTIs such as raltegravir and elvitegravir share a low genetic barrier to resistance, causing the loss of virologic activity in clinical studies (Brooks *et al.*, 2019). In contrast, dolutegravir and bictegravir – two second-generation INSTIs – exhibit a higher genetic barrier to resistance, limited cross-resistance, and less drug-drug interactions (Oliveira *et al.*, 2018; Podany *et al.*, 2017). Currently, the WHO, IAS-USA, and EACS guidelines recommend the use of INSTIs in the first-line HIV regimens (Brooks *et al.*, 2019). Novel INSTIs such as cabotegravir are undergoing clinical development (Orkin *et al.*, 2020).

HIV GP41

GP41 is a transmembrane protein encoded by the env gene. As a key structure protein, HIV GP41 binds with GP120 to form HIV spike trimers on the surface of HIV particles (Mao *et al.*, 2012). During the viral entry, the N-heptad repeat (NHR) and C-heptad repeat (CHR) of GP41 switch to a six-helix bundle (6-HB) structure which binds to the human cell membrane and drives the viral fusion into the human cells. Many antiviral agents have been developed to target the hydrophobic pocket within the NHR trimer, therefore preventing viral entry (Mostashari Rad *et al.*, 2018).

As the only GP41 inhibitor approved by the US FDA, enfuvirtide is a fusion peptide inhibitor that mimics the N-heptad repeat and prevents the formation of the six-helix bundle structure of GP41. Clinical use of enfuvirtide requires twice-daily subcutaneous injection (90 mg/Kg for adults, 2 mg/Kg for children aged 6–16 years) (Kitchen *et al.*, 2008). Enfuvirtide is not commonly used in clinical practice because of its side effects (eosinophilia, neutropenia, increased risk of bacterial pneumonia), its short half-life, and lack of oral availability (Reust, 2011). Although many attempts have been made, the development of GP41 inhibitors remains difficult due to the emerging mutations and structural dynamics of HIV GP41.

HIV GP120

GP120, encoded by the env gene, is an envelope glycoprotein on the surface of HIV particles. During the viral entry, HIV GP120 binds to the CD4 receptor and the CCR5/CXCR4 co-receptor on the surface of human $CD4^+$ T cells (Falkenhagen and Joshi, 2018; Shaik *et al.*, 2019). The Phe43 pocket and other conserved regions on the GP120 are considered as the real targets for developing anti-HIV drugs (Mostashari Rad *et al.*, 2018). The drugs targeting GP120 can be called adhesion inhibitors, mainly blocking the binding of GP120 with CD4 (Pu *et al.*, 2019).

Fostemsavir (BMS-663068) is the first GP120-directed attachment inhibitor approved by the US FDA on July 3rd, 2020. Fostemsavir tromethamine is the prodrug of temsavir – the active moiety that binds to the conserved outer domain of GP120 which is adjacent to the CD4 binding loop (Langley *et al.*, 2015). This binding inhibits the exposure of the chemokine co-receptor binding site and prevents the initial interaction of HIV GP120 with the CD4 receptor on human T cells and other immune cells

(Langley *et al.*, 2015). Fostemsavir is recommended for heavily treatment-experienced adults with multidrug-resistant HIV-1 infections. As the only compound in the class of GP120 drugs, fostemsavir harbors a unique resistance profile and exhibits no cross-resistance with other entry inhibitors (Lataillade *et al.*, 2018).

Hepatitis C Virus (HCV)

HCV NS3/4A Protease

The nonstructural protein 3 (NS3) contains a serine protease domain and a helicase domain at the N-terminal and C-terminal regions, respectively (McGivern *et al.*, 2015). The NS3 protein acts as a serine protease to cleave HCV polyprotein precursor at four junctions (NS3-NS4A, NS4A-NS4B, NS4B-NS5A, NS5A-NS5B) to release 5 viral proteins. As a short 54-amino-acid polypeptide, the nonstructural protein 4A (NS4A) serves as an essential co-factor for the NS3 serine protease in a non-covalent complex. NS3 protease is an attractive drug target because its inhibition can terminate the polyprotein processing and restore interferon gene expression (McGivern *et al.*, 2015). NS3/4A protease inhibitors are a key element of direct-acting antivirals that effectively cure HCV infections by targeting one or more viral proteins (Li and De Clercq, 2017).

As of today, ten NS3/4A protease inhibitors have been approved, including glecaprevir, grazoprevir, paritaprevir, simeprevir, vaniprevir, voxilaprevir, asunaprevir, danoprevir, boceprevir (discontinued), and telaprevir (discontinued) (Li and De Clercq, 2017). Moreover, danoprevir was approved in China to treat patients infected with HCV genotype 1b (Miao *et al.*, 2020). Novel NS3/4A inhibitors such as seraprevir are currently under development. For instance, seraprevir is now evaluated in a phase 3 trial (NCT04001608).

HCV NS5A Phosphoprotein

The nonstructural protein 5A (NS5A) is a zinc-binding and proline-rich hydrophilic phosphoprotein that executes versatile functions in genome replication, viral particle assembly, and human-virus interactions (Ross-Thriepland and Harris, 2015). The NS5A protein in the form of a dimer or multimer localizes to the ER-derived membranes via its amphipathic helix domain. NS5A inhibitors can target the amphipathic helix domain of NS5A dimer to inhibit the conformation of double-membrane vesicles and impair HCV RNA replication factories (Shanmugam *et al.*, 2018).

As of today, six NS5A inhibitors (ombitasvir, elbasvir, velpatasvir, daclatasvir, ledipasvir, pibrentasvir) have been approved by the US FDA. These NS5A inhibitors efficiently block in vitro and in vivo viral replication, though their exact models of drug actions are yet to be elucidated (Ross-Thriepland and Harris, 2015). Moreover, the clinical efficacy of NS5A inhibitors plus other direct-acting antivirals offers more than 90% of sustained virologic responses (Li and De Clercq, 2017). Many experimental NS5A inhibitors such as ravidasvir are still under development. Ravidasvir plus sofosbuvir offered promising virologic response rates in 298 patients infected with HCV genotype 4 (Esmat *et al.*, 2017).

HCV NS5B Polymerase

The nonstructural protein 5B (NS5B) is an RNA-dependent RNA polymerase that is indispensable for HCV RNA synthesis and genome replication. The structure of NS5B consists of three subdomains: "palm", "finger", "thumb", and the hydrophobic membrane anchoring C-terminus. As a promising drug target, the catalytic site of NS5B is encircled by the finger and thumb domains. NS5B inhibitors that alter structural conformation or interfere with viral RNA binding exhibit promising potency to inhibit HCV RNA replication (Kirby *et al.*, 2015).

Two NS5B inhibitors have been approved by the US FDA, including sofosbuvir (GS-7977; formerly PSI-7977) in December 2013 and dasabuvir (ABT-333) in December 2014. The NS5B inhibitors can be mainly divided into either nucleoside inhibitors (e.g., sofosbuvir) or non-nucleoside inhibitors (e.g., dasabuvir) (Li and De Clercq, 2017). On the one hand, nucleoside inhibitors block the viral RNA synthesis by mimicking natural substrates and competing with incoming nucleoside triphosphates at the catalytic site of NS5B (Li and De Clercq, 2017). On the other hand, non-nucleotide inhibitors noncompetitively block the allosteric pockets outside the catalytic site to prevent viral RNA synthesis (Li and De Clercq, 2017). For instance, dasabuvir (Kati *et al.*, 2015), GSK5852 (Voitenleitner *et al.*, 2013), beclabuvir (Gentles *et al.*, 2014), and filibuvir (Fenaux *et al.*, 2013) target the allosteric drug pockets in the palm I, palm II, thumb I, and thumb II domains, respectively. Although only two NS5B inhibitors have been approved, many novel NS5B inhibitors (e.g., beclabuvir) are still under development.

Respiratory Syncytial Virus (RSV)

RSV RNA Polymerase

RSV RNA-dependent RNA polymerase – a complex comprising the viral large polymerase subunit, the phosphoprotein, and the transcription elongation factor M2-1 – plays a critical role in viral mRNA transcription, mRNA capping/methylation, and genome

replication (Fearns and Deval, 2016). The large polymerase subunit harbors the enzymatic domains that produce subgenomic mRNAs, RNA replication, and an antigenome RNA for genome RNA synthesis, while the other proteins act as essential cofactors (Fearns and Deval, 2016). Due to its unique features and essential nature, the large polymerase protein has proved to be a promising drug target for the development of nucleoside and non-nucleoside inhibitors.

As of today, ribavirin is an FDA-approved nucleoside inhibitor that inhibits the activity of RSV RdRp, whereas it is largely discontinued to treat RSV infections due to limited efficacy and risk of serious side effects (Shook and Lin, 2017). Experimental inhibitors such as ALS-8176 and PC786 are still under clinical development. ALS-8176 (lumicitabine) is a nucleoside inhibitor with promising anti-RSV efficacy and safety in phase 2a study (NCT02094365) (DeVincenzo *et al.*, 2015; Wang *et al.*, 2015). PC786 is a potent non-nucleoside inhibitor that blocks RSV type A strains (IC_{50}: <0.09–0.71 nM) and RSV type B strains (IC_{50}: 1.3–50.6 nM) in cell cultures (Coates *et al.*, 2017).

RSV Fusion Glycoprotein

RSV fusion glycoprotein is a class I fusion protein that anchors in the membrane of viral particles via a transmembrane domain (Gilman *et al.*, 2019). During the viral entry, RSV fusion glycoprotein in the trimeric form is undergoing dramatic changes from the metastable prefusion confirmation to the highly stable post-fusion conformation, thereby driving the fusion of viral membrane with the human cell membranes (Gilman *et al.*, 2019). RSV fusion glycoprotein that induces RSV-neutralizing antibody responses is a key antigen for protective immunity (Tang *et al.*, 2019). As a leading target of neutralizing antibodies and vaccines, RSV fusion glycoproteins have conserved sequences across different isolates of RSV type A and B strains (Tang *et al.*, 2019).

As of September 2020, palivizumab that binds to RSV fusion glycoprotein remains the only monoclonal antibody approved for the prevention of RSV infection in high-risk infants. Nevertheless, the clinical application of palivizumab is uncommon because of its low stability and its limited efficacy of 50% (Soto *et al.*, 2020). Ongoing studies are currently evaluating many experimental inhibitors of RSV fusion glycoprotein, including preatovir, ziresovir, sisunatovir, MDT-637, JNJ-53718678, and ALX-0171. For instance, preatovir (GS-5806) efficiently inhibits the fusion glycoprotein of RSV-A (EC_{50}: 0.51 $\pm$ 0.25 nM) and RSV-B (EC_{50}: 0.35 $\pm$ 0.15 nM) strains in cell cultures (Perron *et al.*, 2015), and it has completed clinical phase 2 trials (NCT02135614). Ziresovir is another selective and orally bioavailable inhibitor in phase 3 clinical trial (NCT04231968) (Zheng *et al.*, 2019).

Herpes Simplex Virus (HSV)

HSV DNA Polymerase UL30

HSV DNA replication requires seven viral proteins: (1) an origin binding protein UL9, (2) a single-strand binding protein ICP8; (3) a viral polymerase with two subunits UL30 and UL42; (iv) a helicase-primase complex with three subunits UL5, UL8, and UL52 (Chen *et al.*, 2011). HSV DNA polymerase is a heterodimeric complex with two subunits: (1) the catalytic UL30 subunit which offers both polymerase and proofreading exonuclease activities; (2) the UL42 subunit that promotes processivity by tethering UL30 to viral DNA via its direct DNA binding (Vashishtha and Kuchta, 2015). The UL30 subunit belongs to the B-family of polymerases and forms a typical hand-shaped structure with the catalytic residues (D717, D888) located in the palm domain for dNTP polymerization (Vashishtha and Kuchta, 2015). The UL30 subunit can replicate viral DNA with high fidelity, even in the absence of the UL42 subunit. Due to its indispensable role, the UL30 subunit has been considered as a promising drug target to block viral DNA replication (Zarrouk *et al.*, 2017).

As of September 2020, many UL30 inhibitors such as idoxuridine, brivudine, trifluridine foscarnet, aciclovir, famciclovir, valaciclovir, and penciclovir have been approved for HSV treatment. Because current compounds face the challenge of drug resistance and adverse reactions (Vollmer *et al.*, 2019), many experimental inhibitors such as synguanol (Vollmer *et al.*, 2019), mitoxantrone dihydrochloride (Huang *et al.*, 2019), and PHA767491 (Hou *et al.*, 2017) are under development. For instance, synguanol is a methylenecyclopropane nucleoside analog that competitively inhibits HSV-1 UL30 (IC_{50}: 0.33 $\pm$ 0.16 μM) (Vollmer *et al.*, 2019). Mitoxantrone dihydrochloride inhibits viral DNA synthesis by blocking the transcription of UL30 (IC_{50}: 1.21 μM) (Huang *et al.*, 2019). PHA767491 also inhibits UL30 to reduce the expression of HSV viral genes (UL5, UL8, UL29, UL30, UL42, UL52) (IC_{50}: 1.86 μM) (Hou *et al.*, 2017). Antiviral agents such as pritelivir and amenamevir that target HSV helicase-primase complex are still under development (Poole and James, 2018).

HSV Envelope Protein

Although HSV particles harbor at least 15 envelope proteins, four envelope glycoproteins (gD, gB, gH, gL) play an indispensable role in viral entry into all permissive cell types (Agelidis and Shukla, 2015). The viral entry begins with the binding of gD to a human receptor (nectin-1, herpesvirus entry mediator, or 3-O-sulfated heparan sulfate) (Atanasiu *et al.*, 2018). This gD-receptor binding drives the conformation changes in gD to activate the regulatory proteins gH and gL, leading to the activation of gB into a fusogenic state for membrane fusion (Agelidis and Shukla, 2015).

Docosanol (*n*-docosanol; behenyl alcohol) is a naturally occurring antiherpetic agent approved by the US FDA as a topical treatment for herpes labialis, as well as the over-the-counter medication for cold sores and fever blisters (De Clercq and Li, 2016).

Although its exact mechanism of action remains unclear, docosanol may inhibit the interactions between HSV envelope proteins and human receptors (De Clercq and Li, 2016). Experimental inhibitors such as C19 and NGI-1 are still under development (Rinis *et al.*, 2018; Lu *et al.*, 2019).

Human Cytomegalovirus (HCMV)

HCMV DNA Polymerase UL54

HCMV DNA polymerase is a multiprotein complex that contains a catalytic subunit UL54 and a processivity factor UL44 to synthesize long stretches of viral DNA during viral replication (Appleton *et al.*, 2004). The homodimer UL44 binds to viral DNA to prevent dissociation from the template, thereby promoting the long-chain DNA synthesis within the catalytic subunit of UL54 (Appleton *et al.*, 2004). Due to its essential role in viral DNA synthesis, UL54 has been recognized as an important drug target against HCMV.

As of today, cidofovir, ganciclovir, foscarnet, valganciclovir, and fomivirsen (discontinued) have been approved for HCMV treatment. To inhibit viral DNA synthesis, cidofovir and ganciclovir are converted to DNA polymerase substrate analogs by the thymidine kinase of CMV. UL54 gene is prone to mutations that limit the efficiency of antiviral agents (Chou *et al.*, 2016). Furthermore, cidofovir may induce nephrotoxicity especially in bone marrow transplant patients (Piret *et al.*, 2017), which limits its clinical use. Novel compounds such as CMX001 (brincidofovir) are currently under development. CMX001 can be converted to cidofovir. The drug potency is much higher for CMX001 than for cidofovir. Cidofovir from CMX001 does not accumulate in the kidneys, therefore nephrotoxicity could be greatly reduced during the treatment (Marty *et al.*, 2013).

HCMV Terminase UL56

HCMV DNA terminase complex is a hetero-oligomer composed of UL56, UL89, and additional viral subunits (UL51, UL52, UL77, UL93) (Ligat *et al.*, 2018). This terminase complex cleaves HCMV DNA concatemers and packages the genome into the capsid for the DNA-packing process during the viral maturation and packaging (Ligat *et al.*, 2018). The large terminase subunit UL56 plays an essential role in the viral DNA cleavage and packaging (Ligat *et al.*, 2018). UL56 not only has the ATPase activity that hydrolyzes ATP to provide energy for the genome cutting and transfer activities but also has ATP-independent endonuclease activity driven by UL89 (Ligat *et al.*, 2018). As an indispensable viral protein, UL65 has been considered to be a promising drug target.

As of September 2020, letermovir remains the only UL56 inhibitor approved by the US FDA for preventing HCMV in adult HCMV-seropositive recipients of an allogeneic hematopoietic stem cell transplant. Based on a phase 3 clinical trial (NCT02137772), letermovir prophylaxis significantly reduced the risk of HCMV infection, and its adverse effects were mild (Marty *et al.*, 2017). Moreover, letermovir is a viral DNA-packaging inhibitor, remarkably specific for HCMV, but not other herpesviruses (Ligat *et al.*, 2018).

Human Influenza Virus

Viral RNA Polymerase

The influenza polymerase is comprised of polymerase basic protein 1 (PB1), polymerase basic protein 2 (PB2), plus either polymerase acidic protein (PA) in influenza A/B or polymerase 3 protein (P3) in influenza C/D viruses (Takashita, 2020). The PB1 subunit encodes the RNA-dependent RNA polymerase, while the PA and PB2 subunits offer the endonuclease and cap-binding activities, respectively (Wandzik *et al.*, 2020). During the transcription of viral mRNA, the cap-snatching of capped oligomers from human Pol II transcripts is mediated by the PB2 cap-binding and PA endonuclease activities. Subsequently, the PB1 active site undertakes the prime template-directed RNA synthesis, followed by the initiation, elongation, termination, and recycling of typical polymerase activities (Wandzik *et al.*, 2020). Due to their importance, PA, PB1, and PB2 have been considered as promising antiviral targets.

As of September 2020, the PA inhibitor baloxavir marboxil (S-033188) and the PB1 inhibitor favipiravir (T-705) have been approved for clinical use, while the PB2 inhibitor pimodivir (JNJ-63623872, VX-787) is currently evaluated in phase 3 trials (NCT03381196, NCT03376321). As a pyrazine derivative, favipiravir received conditional marketing approval only for patients with a novel or reemerging influenza when other antivirals are ineffective because favipiravir increases the risk for teratogenicity and embryotoxicity (Takashita, 2020). Baloxavir marboxil was approved for treating influenza A and B viruses, while its pattern of drug susceptibility follows the order: influenza A > B > C > D (Takashita, 2020). As a cyclohexyl carboxylic acid analog, pimodivir inhibits viral RNA binding by occupying the cap-binding domain of PB2, and it shows strong activity against influenza A but not B viruses (Takashita, 2020). Other novel polymerase inhibitors are still under development.

Neuraminidase

Influenza surface glycoprotein neuraminidase is known for its multifunctional roles in viral entry and viral release. During the viral entry, the glycoprotein neuraminidase contributes to the viral binding to the sialic acid receptors of human cell glycoproteins,

Table 1 Summary of viral proteins targeted by approved and novel inhibitors

Human viruses	*Viral targets*	*Approved drugs*	*Novel inhibitors*
Human immunodeficiency virus (HIV)	Protease	Amprenavir, atazanavir, darunavir fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir,	TMB-607, TMC-310911, GRL-09510
	Reverse transcriptase	NRTIs: abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir alafenamide, tenofovir disoproxil fumarate, zidovudine,	MK-8504, MK-8583, racivir, islatravir, rovafovir etalafenamide, censavudine, amdoxovir, elvucitabine,
		NNRTIs: delavirdine[a], doravirine, efavirenz, elsulfavirine[b], etravirine, nevirapine, rilpivirine,	KM-023
	Integrase	Bictegravir, dolutegravir, elvitegravir, raltegravir,	Cabotegravir
	gp41	Albuvirtide[b], enfuvirtide	GSK373239
	gp120	Fostemsavir	
Hepatitis C virus (HCV)	NS3/4A protease	Danoprevir[b], glecaprevir, grazoprevir, paritaprevir, paritaprevir, Simeprevir,	Asunaprevir, faldaprevir furaprevir, narlaprevir, Seraprevir, vaniprevir, vedroprevir
	NS5A phosphoprotein	Daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir, pibrentasvir	Ravidasvir, ruzasvir, odalasvir
	NS5B polymerase	Sofosbuvir, dasabuvir	Adafosbuvir, deleobuvir, Lomibuvir, mericitabine, Radalbuvir, radalbuvir,
Human influenza virus	RNA polymerase	Baloxavir marboxil, favipiravir[b]	Pimodivir (VX-787)
	Neuraminidase	Laninamivir[b], oseltamivir, peramivir, zanamivir,	Isocorilagin
	Matrix protein 2	Amantadine[a], rimantadine	
Respiratory syncytial virus (RSV)	RNA polymerase	Ribavirin	Lumicitabine (ALS-8176)
	Fusion glycoprotein	Palivizumab	Presatovir (GS-5806), ziresovir (RO-0529, AK0529), MDT-637, JNJ-53718678, sisunatovir, ALX-0171
Herpes simplex virus (HSV)	DNA polymerase UL30	Aciclovir, brivudine, famciclovir, foscarnet, idoxuridine, penciclovir trifluridine, valaciclovir	Synguanol, filociclovir, MBX-2168; mitoxantrone dihydrochloride; PHA767491
	Envelope proteins	Docosanol	NGI-1, C19
Human cytomegalovirus (HCMV)	DNA polymerase UL54	Cidofovir, fomivirsen, foscarnet, ganciclovir, valganciclovir,	Filociclovir
	Terminase UL56	Letermovir	
Varicella-zoster virus (VZV)	DNA polymerase	Aciclovir, brivudine, famciclovir, valaciclovir, vidarabine	
Hepatitis B virus (HBV)	DNA polymerase	Adefovir, besifovir[b], clevudine[b] entecavir, telbivudine, tenofovir alafenamide, tenofovir	Tenofovir exalidex
Human smallpox	VP37 envelope wrapping protein	Tecovirimat	

[a]Discontinued.

[b]Elsulfavirine was approved in Russia, albuvirtide was approved in China; favipiravir and laninamivir were approved in Japan; danoprevir was approved in China; clevudine was approved in South Korea and the Philippines; besifovir was approved in South Korea.

leading to the enhancement of hemagglutinin receptor binding (Wen and Wan, 2019). During the viral release, neuraminidase cleaves sialic acids from cellular receptors and neuraminidase/hemagglutinin on nascent influenza virions so as to prevent virion aggregation and release new particles (McAuley *et al.*, 2019). Due to its importance, neuraminidase has been recognized as a promising antiviral target (Kumar *et al.*, 2020).

As of September 2020, neuraminidase inhibitors such as oseltamivir, zanamivir, peramivir, and laninamivir have been approved for clinical use (**Table 1**). Oseltamivir is used orally as the first-line therapy, but its effectiveness is compromised by the development of drug resistance mutations in influenza A genotypes such as H3N2 and H5N1 (Kumar *et al.*, 2020). Due to the emergence of drug resistance, it remains an urgent need to develop anti-influenza agents. Novel antivirals such as A-192558 and A-315675 are still under development (Gubareva and Mohan, 2020).

Matrix Protein 2

The influenza matrix protein 2 (M2) is a 97-residue single-pass membrane protein that forms pH-gated proton channels in the viral lipid envelope (Schnell and Chou, 2008). By shuttling protons inwards and outwards through the viral membrane, matrix protein 2 equilibrates pH across the viral membrane during the viral entry and across the trans-Golgi membrane of host cells during the viral maturation (Mandala *et al.*, 2020). Because the channel pore is essential for the proton shuttling, the pore of the M2 channel is a promising drug-binding pocket (Gu *et al.*, 2013).

As of September 2020, rimantadine and amantadine that target the M2 channel pore have been approved for anti-influenza treatment. For instance, amantadine targets the M2 channel by hydrophobic interactions between the adamantane group and the N-terminal gate of the channel (Gu *et al.*, 2013). Mutations (e.g., V27A, L26F) within the channel pore weaken the hydrophobic interactions of rimantadine and amantadine with the M2 channel, thereby causing drug resistance and treatment failure (Gu *et al.*, 2013). Novel inhibitors that are less prone to mutations may lead to better antiviral efficacy.

Variola Virus (Human Smallpox)

VP37 Envelope Wrapping Protein

The extinction of variola virus, the etiological agent of human smallpox was declared by the WHO in 1980 (Jordan *et al.*, 2010). The F13L gene of variola virus encodes a highly conserved 37 kDa peripheral membrane protein called VP37. Before the viral budding, the wrapping complex requires VP37 and other viral proteins to interact with human membrane proteins; subsequently, it catalyzes the maturation of intracellular viral particles into the egress-competent form of the variola virus particles (Jordan *et al.*, 2010). VP37 interacts with human proteins Rab9 and TIP47 (a Rab9-specific effector) in membrane fractions from infected cells to facilitate assembly of extracellular virus (Chen *et al.*, 2009).

As of September 2020, tecovirimat (ST-246) remains the only VP37 inhibitor approved for treating human smallpox, although its effectiveness has only been shown in animal models but not humans due to the extinction of the virus in human populations. As an 4-trifluoromethyl phenol derivative, tecovirimat blocks the interactions of VP37 with Rab8 and TIP47, thereby inhibiting the maturation of egress-competent enveloped virions for viral budding (Jordan *et al.*, 2010). Novel compounds such as NIOCH-14 are still under development (Delaune and Iseni, 2020).

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

SARS-CoV-2 Polymerase

SARS-CoV-2 RNA-dependent RNA polymerase, encoded by the NSP12 gene, forms a polymerase complex with its viral cofactors NSP7 and NSP8 to catalyze the viral RNA synthesis during the viral replication and transcription (Gao *et al.*, 2020). Similar to SARS-CoV polymerase, the structure of SARS-CoV-2 polymerase contains three subdomains: fingers, a thumb, and a palm, while the catalytic site (S759-D760-D761) is located within the conserved motifs of the palm domain (Gao *et al.*, 2020). The cofactors NSP7 and NSP8 interact with the thumb, while another NSP8 binds to the fingers, thereby conferring processivity to NSP12 (Hillen *et al.*, 2020). Due to its indispensable role in viral RNA replication, SARS-CoV-2 polymerase is an important target for antiviral drug development (Li and De Clercq, 2020; Zhou *et al.*, 2020; Jiang *et al.*, 2020).

As of October 2020, remdesivir (GS-5734) has been authorized in the US for clinical use as a polymerase inhibitor to treat patients infected with SARS-CoV-2. Remdesivir acts as a delayed chain terminator to interfere with the RNA synthesis of viral polymerase and evades the proofreading of viral exoribonuclease (Eastman *et al.*, 2020). The intravenous use of remdesivir could shorten the recovery time and reduce the mortality rate of SARS-CoV-2 based on a randomized, double-blinded, placebo-controlled trial (NCT04280705) (Olalla, 2020). Other novel experimental inhibitors such as GS-441524 (Yan and Muller, 2020) and favipiravir (Arab-Zozani *et al.*, 2020) might offer antiviral activities against SARS-COV-2, but their clinical use requires further investigation.

Varicella Zoster Virus (VZV)

VZV DNA Polymerase

VZV polymerase belongs to the DNA polymerase type-B family. As the essential component of VZV replication complex, DNA polymerase is encoded by the open reading frame 28 (ORF28). VZV DNA polymerase is an ideal target for the development of nucleoside analogs because it plays a critical role in viral DNA replication during the life cycle.

As of September 2020, nucleoside analogs such as aciclovir, famciclovir, valaciclovir, brivudine, and vidarabine have been approved for VZV treatment (De Clercq and Li, 2016). These compounds could effectively target VZV polymerase and block viral DNA synthesis. As a prodrug of penciclovir, famciclovir effectively prevents the recurrence of VZV, and it has only mild adverse events (Wang *et al.*, 2020). Furthermore, both aciclovir and famciclovir interventions offer high rates of benefit and showed a similar time to full crusting of lesions (Pott Junior *et al.*, 2018).

Hepatitis B Virus (HBV)

HBV DNA Polymerase

HBV RNA-dependent DNA-dependent polymerase, encoded by the open reading frame P, acts with multifaceted functions such as (1) HBV reverse transcription that synthesizes the (−) DNA strand from the viral RNA template within the catalytic site of HBV polymerase; (2) degradation of the viral RNA template by the RNase H activity of HBV polymerase (Menendez-Arias *et al.*, 2014). HBV polymerase is mainly comprised of three functional domains: the template domain (AA positions: 1–183), the polymerase domain (349 − 691), and the RNase H domain (692 − 845) (Menendez-Arias *et al.*, 2014). The catalytic site of the polymerase domain is considered as a promising drug target, whilst nucleos(t)ide inhibitors have been developed to compete with the incorporation of natural nucleotide substrates into the elongating DNA chain, thereby blocking viral DNA synthesis (De Clercq and Li, 2016).

As of September 2020, many nucleos(t)ide inhibitors (entecavir, telbivudine, adefovir dipivoxil, tenofovir disoproxil fumarate, tenofovir alafenamide, clevudine, and besifovir) have been approved for clinical use. Note that clevudine was only approved in South Korea and the Philippines, while besifovir was approved in South Korea. Despite the success of nucleos(t)ide inhibitors to suppress the viral replication, they do not eliminate the virus from the hepatocytes, and a cure of HBV infection remains yet to be discovered. Novel HBV polymerase inhibitors such as tenofovir exalidex are still under clinical development (Martinez *et al.*, 2020).

Conclusion

Based on the classification of approved antiviral agents, several features could be summarized. First, antiviral agents mostly target the viral proteins with high specificity, leading to less toxicity compared with human protein targets. Second, among 9 infectious diseases, the most popular drug targets could be listed as follows: viral polymerase, viral envelope glycoproteins, and viral protease. These three viral proteins play a dispensable role in viral replication, making them promising viral targets for most human viruses. Third. antiviral agents are mostly small molecules that can be taken orally in clinical settings, while few antibodies and peptide inhibitors have been approved for antiviral use. Compared with monoclonal antibodies and peptides, small molecules are typically cheaper, chemically stabler, structurally simpler and better permeable.

Although this article only describes 10 infectious diseases with approved drugs, future antiviral development should also focus on emerging infectious diseases such as coronaviruses, dengue, Zika, and Ebola. On October 14, 2020, the US FDA approved a mixture of three monoclonal antibodies (atoltivimab, maftivimab, odesivimab-ebgn), which marks the first FDA approval for the treatment of Ebola virus infection. Furthermore, it remains critical improving antivirals to combat emerging drug resistance mutations because drug resistance mutations have been observed in many viruses (e.g., HIV, HBV, influenza).

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